IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Peter Richardson	Art Unit	: 1623
Serial No.	: 10/537,564	Examiner	: Lawrence E. Crane, Ph.D.
Filed	: August 28, 2006	Conf. No.	: 4551
Title	: USE OF SPONGOSINE FOR THE TREATMENT OF PAIN		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF PETER RICHARDSON UNDER 37 CFR § 1.132

Peter Richardson declares as follows:

1. I have BA in Biochemistry from the University of Oxford (1976), a MA from the University of Oxford (1979) and a Ph.D. in Biochemistry from the University of Cambridge (1979). My *curriculum vitae* is attached.

2. I am an inventor of the above-captioned patent application.

3. I supervised a study which found that spongosine can reduce inflammatory and neuropathic pain in animals at a dose of 0.4 mg/kg. I also supervised a study which found that spongosine can reduce diabetic neuropathic pain in humans at a dose of 0.1mg/kg. These results are completely unexpected because the dosages used result in a peak maximum plasma concentration of about 0.2 micromolar, an order of magnitude below the Kd for spongosine at the A2A adenosine receptor (about 2.0 micromolar). One would expect that at a plasma concentration so far below the Kd of spongosine for the A1 and A2A adenosine receptors, spongosine would not activate either receptor and thus would not have an analgesic effect. Also, surprisingly, additional studies using animal models of inflammatory and neuropathic pain

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found that maintained plasma concentrations of 0.02 micromolar (i.e., 1% of the value required to activate A2A receptors in tissues) are effective in reducing pain.

4. Without being bound by any particular theory, it appears that in certain tissues, such as epithelia, tissue damaged by physical, chemical or biological trauma, and those tissues undergoing an inflammatory response, the pH is lower than that of other tissues. The lower pH alters the binding affinity of spongosine for adenosine receptors such that spongosine is selective for the A2A adenosine receptor in such tissues. This allows the unexpected alleviation of pain and inflammation by spongosine at a plasma concentration that is too low to activate A1 and A2A adenosine receptors in other tissues thereby avoiding such negative side-effects as bradycardia and hypotension respectively.

5. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issued thereon.

Date: 19/Dec/2009

Peter Richardson, Ph.D.